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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,901	06/07/2006	Anders Lindahl	1034005-000021	9242

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
01/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/581,901	LINDAHL ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-16 and 19-37* is/are pending in the application.

4a) Of the above claim(s) *9-12,28-31 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,13-16,19-27 and 32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06/07/2006* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/21/2008, 09/01/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group I, claims 1-6,8,13-16,19-27 and 32-36 in the reply filed on 11/21/2008 is acknowledged.

Claims 9-12,28-31, and 37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/21/2008.

Claim Objections

Claims 1-6,8,13-16,19-27 and 32-36 are objected to because they read on nonelected subject matter. The claims fail to require that the cells to be cultured be hBS cells and not hBS-derived cells, the latter of which are subject matter of Group II in the restriction dated 06/23/2008. Furthermore, the claims do not require the cells remain undifferentiated and thereby further encompass methodology associated with non-elected Group II. The instant office action relates only to clonal derivation of hBS cells that remain pluripotent. The rejections herein may not be applicable to the nonelected group and, conversely, additional rejections may be necessary over the non-elected group. Thus, Applicant should remove recitation of use of hBS-derived cells and require maintenance of pluripotency.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6,8,13-16,19-27 and 32-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of clonal derivation of pluripotent human blastocyst-derived stem cell lines comprising subjecting hBS cell colonies to non-enzymatic treatment in the

presence of a chelator to dissociate the cell colonies into one or more single cells, selecting/picking of one or more single cells, separately culturing the one or more single cells in hBS conditioned medium and in fibroblast feeder conditioned serum-based medium or on a fibroblast feeder layer in serum based medium, and optionally changing the medium to a serum free medium to obtain one or more pluripotent hBS cells does not reasonably provide enablement for 1) dissociation into single cells without the use of a chelator or 2) culture of clonally-derived cells in the absence of hBS conditioned medium or 3) culturing blastocyst-derived stem cell lines in the absence of a fibroblast feeder cell layer or fibroblast conditioned medium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Nature of the Invention. The invention involves methods of obtaining clonally-derived pluripotent human blastocyst-derived stem cell lines by using isolating the inner cell mass cells of a human blastocyst by mechanical dissection in medium containing EDTA, and co-culturing the inner cell mass cells with conditioned serum-based media to obtain a clonal blastocyst-derived stem cell line.

Breadth of the claims. The claims are broad in that they fail to recite requirements for the culture media for clonal hBS cells. Claims 4 and 23 recite specific media, however, only one of those recited is conditioned by hBS cells. Thus, no claims are limited to use of hBS conditioned medium. The claims also are broad in that they fail to require either a fibroblast feeder layer of fibroblast conditioned medium to prevent the differentiation of cells. Thus, the claims encompass culture without fibroblast feeders or fibroblast conidtioined medium. Finally, the claims are broad in that they encompass dissociation of hBS colnies into single cells without the addition of EDTA to the medium.

Guidance of the Specification/The Existence of Working Examples. The specification provides guidance with regard to the generating of clonally-derived human pluripotent blastocyst-derived stem cell lines. The specification teaches that glass capillaries were used to transfer the inner part of hBS colonies to a solution with EDTA, a chelator (Example 4, page 14). The cells were triturated with a pipette and diluted in medium. Single cells were then transferred individually to mEF coated plates in the presence of hBS conditioned, serum-containing media. The specification teaches that use of hBS conditioned media prevents the death and differentiation associated with clonal culture of hBS cells (page 15). The specification teaches that culture conditions may be rate limiting for maintaining the undifferentiated state of hBS cell include mEF density and quality (page 15). Thus, clonal lines were expanded on mEF layers (Example 5) in the presence of hBS conditioned medium. The specification also teaches fibroblast conditioned medium (see page 13, Examples 1-3). The specification teaches that concentrated conditioned medium (CC) is medium that has been cultured with mEF cells, and while claim 4 recites use of CC-medium, it fails to require it. The specification does not teach propagation of clonal hBS cells in

the absence of hBS conditioned media. The specification does not teach culture of the hBS cells without feeder layers or conditioned medium.

The specification teaches use of a chelator in dissociating cell colonies (Example 4). At page 5, the specification teaches a chelator as a substitute for enzymatic treatment in dissociating cell-cell interactions without over-digesting the cell membrane. The specification does not teach obtaining single cells without use of a chelator.

State of the Art/Predictability of the Art. The state of the art at the time of filing was that clonal lines of human ES cells were very difficult to derive. Ellerstrom taught that hESCs depend on cell-cell interactions as well as paracrine/autocrine signals for survival at clonal density (2007, **Stem Cells**, 25:1690-1696). Factors must be provided in the media to maintain the pluripotent state of hES cells when they are dissociated into single cells (see Pyle, 2006, **Nature Biotechnology**, 24:344-350). Pyle found that neurotrophins were able to support high efficiency clonal survival of hES cells. Thus, clonal propagation of hES cells in the absence of certain factors that were yet to be discovered at filing was highly unpredictable. See also, Joannides et al, **Stem Cells,** 2006 Feb;24(2):230-5 and Watanabe, 2007, IDS.

Furthermore, the state of the art of culturing of primate embryonic stem cells is such that culturing typically requires the presence of feeder cells. Thomson *et al.* discuss the difficulties in culturing pPS in feeder free conditions. Thomson *et al.* (**PNAS**, 1995, 92: 7844-7848) teach the derivation of a cloned cell line from a rhesus monkey that remains undifferentiated when grown on mouse embryonic fibroblast feeder layers, but differentiate or die in the absence of the fibroblasts (see p. 7844, *Abstract*). Particularly, Thomson *et al.* state that in the absence of the feeder layers, soluble human leukemia inhibitory factor (LIF) fails to prevent the differentiation of the cells, and that the factors that fibroblasts produce to prevent the differentiation of the cells is yet unknown (see p. 7847, 1st column, 2nd paragraph). Thomson *et al.* further state that human inner cell mass-derived cells were cultured in the

absence of feeder layers failed to survive beyond 2 passages (see p. 7848, 1st paragraph).

The requirement for human ES cells to be cultured on fibroblast feeder cells is additionally supported by Thomson *et al.* (**Tibtech**, 18:53-57, 2000), who state that, "The critical factors produced by the fibroblast feeder layers that prevent differentiation of human ES cells and EG cells are unknown … Human ES cells cultured in the presence of LIF and absence of fibroblasts uniformly differentiate or die within 1-2 weeks." See page 54, 2nd col., 2nd **full ¶**, emphasis added.

Further, the state of the art of culturing ES cells is unpredictable. Lim *et al.* [**Proteomics**, 2:1187-1203(2002)] teach the proteome analysis of conditioned medium from mouse embryonic fibroblast feeder layers to characterize the environment that supports the growth of undifferentiated human ES cells, and to identify factors critical for their independent growth. See *Abstract*. Lim state that, "Despite many years of using mouse embryonic fibroblast cells as feeder support of human ES cells, it is still not clear what these cells for their clients. The interaction between these two cell types might take place *via* factors secreted into the medium or into extracellular matrix as well as through membrane-bound proteins." See p. 1188, 1st ¶. Lim teach that by utilizing proteomic analysis, unexpected results identify many known intracellular proteins, and that further analysis using serum-containing medium in the presence of ES cells, and using other cell types for feeder layers will be required. See p. 1203, 1st ¶, #4.

The Amount of Experimentation Necessary. The instant specification only provides guidance for culturing the human blastocyst-derived stem cells on fibroblast feeder layers. Furthermore, the state of the art teaches that it would not be predictable that hBS cells could be maintained in an undifferentiated state in the absence of feeder cells or feeder-conditioned medium. As specific factors produced by fibroblasts that support undifferentiated growth of hES cells have yet to be identified, it would not be predictable one of skill in the art could culture the claimed hBS in the absence of feeders and maintain the human blastocyst-derived stem cells in an undifferentiated state.

Accordingly, in view of the teachings of the state of the art with regard to the culturing of hBS cells, the lack of direction or guidance provided by the specification for culturing the undifferentiated human blastocyst-derived stem cells in the absence of feeders and clonal cells in the absence of hBS conditioned medium, in order to maintain the hBS cells in a viable and undifferentiated state, it would have required undue experimentation for one of skill in the art to carry out the claimed methods.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4,13,23 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 23 recite "in a suitable medium, such as,. . .". Use of "such as" in this case renders the claim indefinite because it recites 3 possibilities for suitable media but it is not clear what the metes and bounds of "suitable medium" are. The specification teaches only the three listed in the claim so it is not clear if these are the only media intended to be suitable or if there are other suitable medias.

Claims 13 and 32 are unclear as they require use of a medium that promotes propagation. It's not clear, in light of the elected invention, what else claim 1 could encompass other than propagation. Claim 13 infers that claim 1 encompasses cultivation to cause differentiation, which is not elected. Culture of pluripotent hBS cells, by definition, is propagation. Thus, it is not clear what is intended by claim 13, which renders the metes and bounds of claim 1 unclear.

Conclusion

The claims appear to be free of the prior art. At the time of filing, hBS colonies were mechanically dissociated into small clumps. The art taught chemical treatment to obtain single hBS cells. However, the art also taught against single cell isolation of hBS cells as the cell-cell interactions were necessary in the absence of specific factors that had yet to be revealed. The art also taught the labor intensive nature of mechanical dissection even into small clumps was a drawback. Thus, the inability to automate mechanical isolation in addition to the inefficiency of clonal culture, appear to cause the claims to fall short of meeting the requirements of 35 USC 103. However, the novelty of the invention appears to be culture in hBS media, to overcome the unpredictabilities of the art and is not recited in the claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner, Art Unit 1632